IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIOVAIL LABORATORIES INTERNATIONAL SRL a corporation of Barbados, Plaintiff, v. ANDRX PHARMACEUTICALS, LLC and ANDRX CORPORATION, Defendants.	)	C.A. Nos. 05-586 (GMS) 05-730 (GMS) 06-620 (GMS) (CONSOLIDATED) **REDACTED - PUBLIC VERSION**

JOINT APPENDIX OF INTRINSIC AND EXTRINSIC EVIDENCE
(VOLUME 3 OF 3)

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JOINT APPENDIX OF INTRINSIC AND EXTRINSIC EVIDENCE

EXHIBIT 18

GUIDANCE[1]

ORAL EXTENDED (CONTROLLED) RELEASE

DOSAGE FORMS

IN VIVO BIOEQUIVALENCE

AND *IN VITRO* DISSOLUTION TESTING

I. PURPOSE OF GUIDANCE

This guidance describes *in vivo* bioequivalence studies and *in vitro* dissolution testing recommended to applicants intending to submit Abbreviated New Drug Applications (ANDA's) for extended release products administered orally.

II. DEFINITION OF TERMS

Terms to describe formulations that do not release the active drug substance immediately following oral administration include modified/extended release (USP XXII), modified/delayed (USP XXII), controlled release, prolonged action, and sustained release. This document uses the term *extended release* to describe a formulation that does not release active drug substance immediately after oral dosing and that also allows a reduction in dosage frequency. This nomenclature accords generally with the USP definition of modified/extended release but does not specify an impact on dosing frequency. The terms *controlled release* and *extended release* are considered interchangeable in this guidance. The guidance does not consider bioequivalence studies for

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[1] This statement, prepared by the Division of Bioequivalence in the Office of Generic Drugs, is an informal communication under 21 CFR 10.90 (b) (9) that represents the best judgment of the division at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research, Food and Drug Administration, to the views expressed. For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (phone: 301-594-2290; FAX: 301-594-0181).

modified/delayed release formulations. A glossary of these terms used in the guidance appears in Attachment 1.

III. REGULATORY BACKGROUND AND GENERAL REQUIREMENTS

The Drug Price Competition and Patent Term Restoration Act amendments of 1984 to the Food, Drug and Cosmetic Act gave the Food and Drug Administration statutory authority to accept and approve for marketing ANDA's for generic substitutes of pioneer products, including those approved after 1962. To gain approval, ANDA's for a generic extended release formulation must, among other things, be both pharmaceutically equivalent and bioequivalent to the pioneer extended release product, which is also termed the reference listed product as identified in FDA's *Approved Drug Products with Therapeutic Equivalence Ratings* (*The Orange Book*).

A. Pharmaceutical Equivalence

To be pharmaceutically equivalent, the generic and pioneer formulations must 1) contain the same active ingredient; 2) contain the same strength of the active ingredient in the same dosage form; 3) be intended for the same route of administration; and 4) generally be labeled for the same conditions of use. FDA does not require that the generic and reference listed extended release products contain the same excipients, or that the mechanism by which the release of the active drug substance from the formulation be the same.

B. Bioequivalence Studies

1. *In Vivo* Bioequivalence Studies for Approval

Current regulations require that bioequivalence be demonstrated between a generic extended release formulation and the reference listed product. The reference listed product is generally an extended release product subject to an approved full New Drug Application (NDA). For approval, documentation of bioequivalence must be established through performance of a series of *in vivo* bioequivalence studies that are defined in Section IV of the guidance. Approval of an ANDA will rely on data derived from evaluation of a biobatch, which is to be manufactured in accordance with the Office of Generic Drugs

Procedure and Policy Guide 22-90.

2. *In Vitro* Dissolution for Quality Control (Pre-Approval Submission of Data Required)

Quality control of the manufacture of an extended release formulation after approval may be assessed, in part, through performance of *in vitro* dissolution tests. Recommendations for the conditions under which this test may be performed are described in Section V. This section also describes how specifications for this test are developed by the applicant and approved by the Division of Bioequivalence. These data are required in the application for approval.

IV. *IN VIVO* BIOEQUIVALENCE STUDIES FOR APPROVAL

In vivo bioequivalence studies recommended for approval for extended release generic formulations are designed to document that:

- The drug product meets the extended release claim made for it.
- The drug product does not release the active drug substance at too rapid a rate (dose dump).
- Performance is equivalent between the generic and the reference listed product following single doses and dosing to steady state.
- The impact of food on the *in vivo* performance is comparable for the generic formulation relative to the innovator formulation.

The above objectives are generally met by the following three *in vivo* studies:

- A single dose, randomized, two-period, two-treatment, two-sequence crossover study under fasting conditions, comparing equal doses of the test and reference products.
- A single dose, randomized, three-treatment, three-period, six sequence, crossover, limited food effects study, comparing equal doses of the test product

administered under fasting conditions with those of the test and reference products administered immediately after a standard breakfast.

- A multiple dose, steady state, randomized, two-treatment, two-period, two-sequence crossover study under fasting conditions comparing equal doses of the test and reference formulations. For safety reasons, this study may be performed in the non-fasting state. Applicants are encouraged to submit a study protocol describing the safety considerations requiring deviation from the fasting state to the Division of Bioequivalence for review prior to execution of the study.

These studies are described in detail in Sections A, B and C below. Under certain circumstances, the Division of Bioequivalence in the Office of Generic Drugs may require additional single dose and/or multiple dose steady state studies. The following general information relative to the three *in vivo* studies is provided:

- FDA designated reference product is identified by the symbol "+" in *The Orange Book*.

- The assayed potency of the test product should not differ from that of the reference product by more than 5%.

- The clinical laboratory conducting any *in vivo* study should retain an appropriately identified reserve sample of the test and reference products for a period of five years. Each reserve sample should consist of at least 200 dosage units. For more information on retention of bioequivalence samples please refer to 21 CFR 320.63.

- A single dose two-way crossover study under fasting conditions is required for each strength of a generic extended release tablet formulation with multiple strengths. The multiple dose steady state study and the food/fasting single dose three-way crossover study are to be conducted with the highest strength only.

  For extended release capsule formulation marketed in multiple strengths, a single dose bioequivalence study under fasting conditions is required only on the highest strength, provided that the compositions of the

lower strengths are proportional to that of the highest strength, and the capsules contain identical beads or pellets. Single dose *in vivo* bioequivalence studies may be waived for the lower strengths on the basis of acceptable dissolution profiles. Multiple dose steady state and single dose food/fasting studies are to be conducted on the highest strength of the capsule formulation.

A. Single Dose Fasting Two-way Crossover Bioequivalence Study

Objective: To compare the rate and extent of absorption of a generic formulation with that of a listed reference formulation when administered in equal labeled doses.

Design: The study design is a single dose, two-treatment, two-period, two-sequence crossover with an adequate washout period (usually equal to at least 10 elimination half-lives of the drug) between the two phases of the study. Equal number of subjects should be randomly assigned to the two possible dosing sequences. The proposed protocol for the study should be approved by an institutional review board prior to initiation of the study.

Facilities: The clinical and analytical facilities used for the study should be identified along with the names, titles, and curriculum vitae of the medical and scientific/analytical directors.

Selection of Subjects: The applicant should enroll a number of subjects sufficient to ensure adequate statistical results. It is recommended that a minimum of 24 subjects be used in this study. More subjects may be required for a drug that exhibits high intra-subject variability in metrics of rate and extent of absorption. Subjects should be healthy volunteers, 18 to 50 years of age, and within 10% of ideal body weight for height and build (Metropolitan Life Insurance Company Statistical Bulletin, 1983). The selection of subjects to enter the study should be based on acceptable medical history, physical examination, and clinical laboratory tests. Subjects with any current or past medical condition which might significantly affect their response to the administered drug should be excluded from the study. Written, informed consent

must be obtained from all subjects before their acceptance into the study.

Procedure: Following an overnight fast of at least 10 hours, subjects should be administered a single dose of the test or reference product with 240 ml water. They should continue fasting for four hours after administration of the test or reference treatment.

Restrictions: Study volunteers should observe the following restrictions:

a. No alcohol or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

b. Subjects should take no prescription medications two weeks prior to and OTC drugs one week before initiation of the study, and until after the study is completed.

c. Drinking water is not allowed from 1 hour pre-dose to 1 hour post-dose except that needed for drug dosing.

d. All meals during the study should be standardized.

Blood Sampling: In addition to the pre-dose (0 hour) sample, venous blood samples should be collected post-dose so that there are at least four sampling time points on the ascending part and six or more on the descending part of the concentration-time curve. The biological matrix (plasma, serum or whole blood) should be immediately frozen after collection and, as appropriate, centrifugation, and kept frozen until assayed.

Analysis of Blood Samples: The active ingredient should be assayed using a suitable analytical method validated with regard to specificity, accuracy, precision (both within and between days), limit of quantitation, linearity, and recovery. Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. If the analytical method is a chromatographic method, chromatograms of unknown samples, including all associated standard curve and quality control chromatograms, should be

submitted for one fifth of subjects, chosen at random.

Pharmacokinetic Analysis of Data: Calculation of area under the plasma concentration-time curve to the last quantifiable concentration (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$), C_{max}, and T_{max} should be performed according to standard techniques.

Statistical Analysis of Pharmacokinetic Data: The log transformed AUC and C_{max} data should be analyzed statistically using analysis of variance. These two parameters for the test product should be shown to be within 80-125% of the reference product using the 90% confidence interval. See also Division of Bioequivalence Guidance *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design*.

Clinical Report and Adverse Reactions: Subject medical histories, physical examination reports, and all incidents of adverse reactions to the study formulations should be reported.

B. Multiple Dose Steady State, Two-Way Crossover Bioequivalence Study under Fasting Conditions.

Objective: To document that the steady state rate and extent of absorption of the test extended release product is similar to the rate and extent of absorption of the reference listed drug containing the same amount of the active ingredient in the same dosage formulation.

Design: The study design is a multiple dose, two-treatment, two-period, two-sequence crossover with adequate washout period between the two phases of the study. Equal number of subjects should be randomly assigned to the two possible dosing sequences. Before initiation of the study, the study protocol should be approved by an institutional review board.

Facilities: See under IV/A.

Selection of Subjects: See under IV/A.

Procedures: Extended release products which are administered once a day should be dosed following an

overnight fast of at least 10 hours; subjects should continue fasting for 4 hours post-dose. For extended release products which are dosed every 12 hours (b.i.d.), the morning dose should be given following an overnight fast of about 10 hours, and subjects should continue fasting for 4 hours post-dose; the evening dose should be administered after a fast of at least 2 hours and subjects should continue fasting for 2 hours post-dose. Each dose should be administered with 240 ml water.

Restrictions: Study volunteers should observe the following restrictions:

a. No alcohol or xanthine-containing foods or beverages should be consumed by subjects for 48 hours prior to dosing and until after the last blood sample is collected.

b. Subjects should take no prescription medications beginning two weeks prior to and OTC drugs one week before the initiation of the study until after the study is completed.

c Drinking water is not allowed from 1 hour pre-dose to 1 hour post-dose except that needed for dosing.

Blood Sampling: At least three trough concentrations (C_{min}) on three consecutive days should be determined to ascertain that the subjects are at steady state prior to measurement of rate and extent of absorption after a single dose administration in a dosing interval at steady state. The three consecutive trough samples should be collected at the same time of the day and should be comparable. For extended release drug products administered more often than every 24 hours, assessment of trough levels just prior to two consecutive doses is not recommended because a difference in the consecutive trough values may occur due to circadian rhythm irrespective of whether or not steady state has been attained. Adequate blood samples should be collected at appropriate times during a dosing interval at steady state to permit estimation of the total area under the concentration-time curve, peak concentration (C_{max}), and time to peak concentration (T_{max}).

Analytical Method: See under IV/A.

Pharmacokinetic Data: The following pharmacokinetic data are to be reported for the evaluation of bioequivalence of the generic extended release product with the reference listed product:

a. Individual and mean blood drug concentration levels

b. Individual and mean trough levels (C_{min})

c. Individual and mean peak levels (C_{max})

d. Calculation of individual and mean steady state $AUC_{interdose}$ are recommended ($AUC_{interdose}$ is AUC during a dosing interval at steady state)

e. Individual and mean percent fluctuation [= 100 * $(C_{max} - C_{min})/C_{min}$]

f. Individual and mean time to peak concentration (T_{max}).

Statistical Analysis of Pharmacokinetic Data: The log transformed AUC and C_{max} data should be analyzed statistically using analysis of variance. These two parameters for the test product should be shown to be within 80-125% of the reference product using the 90% confidence interval. Fluctuation for the test product should be evaluated for comparability with that for the reference product. For further information on statistical analysis, see the Division of Bioequivalence Guidance *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design*.

Clinical Report and Adverse Reactions: See under IV/A.

C. Single Dose, Three-Way Crossover Food/Fasting Study.

Objective: To document that the rate and extent of absorption of the generic extended release product is equivalent to the rate and extent of absorption of the listed reference drug when both products are administered immediately after a high fat content meal [2]

[2] Each subject should consume a standardized, high fat content meal consisting of :

and to assess the effect of high fat content meal on the bioavailability of the generic extended release product.

Design: The study design is a single dose, three-treatment, three-period crossover with adequate washout period between the three phases of the study. Equal number of subjects should be randomly assigned to each of the six dosing sequences.

Selection of Subjects: A minimum of 18 subjects should be enrolled in this study. For other information on selection of subjects see under IV/A.

Procedure: Each subject should receive the following three treatments:

Treatment 1: Generic extended release product administered after a high fat content breakfast.

Treatment 2: Pioneer extended release product (reference listed drug) administered after a high fat content breakfast.

Treatment 3: Generic extended release product administered after fasting.

Following an overnight fast of at least 10 hours subjects receiving the treatment under food challenge conditions should be served a high fat content breakfast, then immediately dosed with Treatment 1 or 2 above with 240 ml water. Subjects receiving Treatment 3 should be dosed at the same time as Treatments 1 and 2 with 240 ml water only. No food should be allowed for at least 4 hours post-dose, with water allowed after the first hour. Subjects should be served standardized meals beginning at four hours during the study.

Restrictions: See under IV/A.

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one buttered English muffin
one fried egg
one slice of American cheese
one slice of Canadian bacon
one serving of hash brown potatoes
eight fluid oz. (240 mL) of whole milk
six fluid oz.(180 mL) of orange juice

Blood Sampling: See under IV/A.

Analysis of Blood Samples: See under IV/A.

Statistical Analysis: In general a comparable food effect will be assumed if the mean values of AUC $_{0-t}$, $AUC_{0-\infty}$, and C_{max} for the generic product administered with food differ by no more than 20% from the respective mean values for the reference listed product administered with food in the study.

V. *IN VITRO* DISSOLUTION FOR QUALITY CONTROL PRE-APPROVAL

A. Dissolution Testing

Dissolution testing should be conducted on 12 individual dosage units of the test and reference products used in the bioequivalence studies. The potential for pH dependence of drug release from an extended release product is well recognized. Dissolution profiles should therefore be generated in aqueous media of the following pH ranges: 1 - 1.5, 4 - 4.5, 6 - 6.5, and 7 - 7.5. Early sampling times of 1, 2, and 4 hours should be included in the sampling schedule to provide assurance against premature release of the drug (dose dumping) from the formulation. The general dissolution conditions to be followed are shown below:

1.	Apparatus	USP XXII Apparatus 1 (rotating basket) for capsules USP XXII Apparatus 2 (paddle) for tablets
2.	Rotation Speed	100 rpm (basket) 50 and 75 rpm (paddle)
3.	Temperature	37 ± 0.5°C
4.	Units To Be Tested	12
5.	Dissolution Medium	900 ml of aqueous media of various pH
6.	Sampling Schedule	1, 2, 4 hours, and every two hours thereafter,

		until 80% of the drug is released.
7.	Tolerances	As established.
8.	Content Uniformity	Content uniformity testing of the test product lot should be performed as described in the USP XXII.

B. Specifications

Specifications for the dissolution procedure to assure quality control will be determined on a case by case basis (usp case 3). In general further validation will be required to expand dissolution specifications beyond those established for the biobatch.

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ATTACHMENT 1

Glossary

Delayed release dosage form :

A delayed release dosage form is one that releases a drug(or drugs) at a time other than promptly after administration.

Extended release dosage form:

An extended release dosage form is one that allows at least a twofold reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g. as a solution or prompt drug-releasing, conventional solid dosage form).

Modified release dosage form:

A modified release dosage form is one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms. Delayed release and extended release dosage forms are two types of modified release dosage forms.

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EXHIBIT 19

JUL 1 1992

GUIDANCE[1]

STATISTICAL PROCEDURES FOR BIOEQUIVALENCE STUDIES USING A STANDARD TWO-TREATMENT CROSSOVER DESIGN

I. INTRODUCTION

The Division of Bioequivalence in the Office of Generic Drugs usually evaluates bioequivalence by comparing the *in vivo* rate and extent of drug absorption of a test and reference formulation in healthy subjects. In a standard *in vivo* bioequivalence study design, study participants receive test and reference products on separate occasions, in either single or multiple doses, with random assignment to the two possible sequences of product administration. Samples of an accessible biologic fluid such as blood or urine are analyzed for drug and/or metabolite(s) concentrations, and pharmacokinetic parameters (AUC, C_{max} and T_{max}) are obtained from the resulting concentration-time curves. These pharmacokinetic parameters are then analyzed statistically to determine if the test and reference products yield comparable values.

Standard statistical methodology based on the null hypothesis is not appropriate to assess bioequivalence (1). The Division of Bioequivalence has therefore employed a testing procedure termed the two one-sided tests procedure (2) to determine whether average values for pharmacokinetic parameters measured after administration of the test and reference products are comparable. This procedure involves the calculation of a confidence interval (3) for the ratio (or difference) between the test and reference product pharmacokinetic variable averages. The limits of the observed confidence interval must fall within a pre-determined range for the ratio (or difference) of the product averages. The determination of the confidence interval range and the statistical level of

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[1]This statement, prepared by the Division of Bioequivalence, Office of Generic Drugs (OGD), in consultation with the Division of Biometrics, Office of Epidemiology and Biostatistics, is an informal communication under 21 CFR 10.90 (b)(9) that represents the best judgment of the Division of Bioequivalence and the Office at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), and does not bind or obligate CDER, FDA, to the views expressed. For information about this guidance, please contact the Division of Bioequivalence (HFD-650), 7500 Standish Place, Metro Park North II, Rockville, MD 20855 (Tel: 301-295-8290; Fax: 301-295-8183).

significance are judgments made by the Division of Bioequivalence.

This Guidance provides information about general pharmacokinetic and statistical analyses of bioequivalence data to be conducted by sponsors of abbreviated new drug and antibiotic applications and addresses three specific aspects of the statistical analysis as follows:

1. Logarithmic transformation of pharmacokinetic data

2. Sequence effect

3. Outlier consideration

This Guidance becomes effective July 1, 1992. Any investigations initiated after that date should generally conform to the recommendations of the Guidance. Sponsors following a different approach are encouraged to discuss the matter in advance with FDA to prevent the expenditure of money and effort on preparing a submission that may later be determined to be unacceptable.

II. GENERAL METHODOLOGY

A. Pharmacokinetic Analysis

1. Single Dose Studies

At a minimum, the following pharmacokinetic parameters for the substance(s) of interest should be measured in a single dose bioequivalence study:

a. Area under the plasma/blood concentration - time curve from time zero to time t (AUC_{0-t}), calculated by the trapezoidal rule, where t is the last measurable time point.

b. Area under the plasma/blood concentration - time curve from time zero to time infinity ($AUC_{0-\infty}$), where $AUC_{0-\infty} = AUC_t + C_t/\lambda_z$, C_t is the last measurable drug concentration and λ_z is the terminal elimination rate constant calculated according to an appropriate method. The terminal or elimination half-life of the drug ($t_{1/2}$) should also be reported.

c. Peak drug concentration (C_{max}) and the time to peak drug concentration (T_{max}), obtained directly from the data without interpolation.

2. Multiple Dose Studies

At a minimum, the following pharmacokinetic parameters for the substance(s) of interest should be measured in a multiple dose bioequivalence study:

a. Area under the plasma/blood concentration - time curve from time zero to time τ over a dosing interval at steady state ($AUC_{0-\tau}$), where τ is the dosing interval.

b. Peak drug concentration (C_{max}) and the time to peak drug concentration (T_{max}), obtained directly from the data without interpolation, after the last dose is administered.

c. Drug concentrations at the end of each dosing interval during steady state (C_{min}).

d. Average drug concentration at steady state (C_{av}), where $C_{av} = AUC_{0-\tau}/\tau$.

e. Degree of fluctuation (DF) at steady state, where $DF = 100\% \times (C_{max} - C_{min})/C_{av}$.

Evidence of attainment of steady state for the test and reference products should be submitted in the bioequivalence study report.

B. Statistical Analysis

Parametric (normal-theory) general linear model procedures are recommended for the analysis of pharmacokinetic data derived from *in vivo* bioequivalence studies. An analysis of variance (ANOVA) should be performed on the pharmacokinetic parameters AUC and C_{max} using General Linear Models (GLM) procedures of SAS (4) or an equivalent program. Appropriate statistical models pertaining to the design of the bioequivalence study should be employed. For example, for a conventional two-treatment, two-period, two-sequence (2 X 2) randomized crossover study design, the statistical model often includes factors accounting for the following sources of variation:

1. Sequence (sometimes called Group or Order)

2. Subjects, nested in sequences

3. Period (or Phase)

4. Treatment (sometimes called Drug or Formulation)

The sequence effect should be tested using the [subject(sequence)] mean square from the ANOVA as an error term. All other main effects should be tested against the residual error (error mean square) from the ANOVA. The LSMEANS statement should be used to calculate least squares means for treatments. The ESTIMATE statement in SAS should be used to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences.

The two one-sided hypotheses at the $\alpha = 0.05$ level of significance should be tested for AUC and C_{max} by constructing the 90% confidence interval for the ratio between the test and reference averages.

III. LOGARITHMIC TRANSFORMATION OF PHARMACOKINETIC DATA

A. Statistical Assumptions

The assumptions underlying the ANOVA are (5):

1. Randomization of samples

2. Homogeneity of variances

3. Additivity (linearity) of the statistical model

4. Independency and normality of residuals

In bioequivalence studies, these assumptions can be interpreted as follows:

1. The subjects chosen for the study should be randomly assigned to the sequences of the study.

2. The variances associated with the two treatments, as well as between the sequence groups, should be equal or at least comparable.

3. The main effects of the statistical model, such as subject, sequence, period and treatment effect for a standard 2 X 2 crossover study, should be additive. There should be no interactions between these effects.

4. The residuals of the model should be independently and normally distributed. In other words, data from bioequivalence studies should have a normal distribution.

If these assumptions are not met, additional steps should be taken prior to the ANOVA including data transformation to improve the fit of the assumptions or use of a nonparametric statistical test in place of ANOVA. However, the normality and constant variance assumptions in the ANOVA model are known to be relatively robust, i.e., small or moderate departure from each (or both) of these assumptions will not have a significant effect on the final result.

B. Rationale for Log Transformation

1. Clinical Rationale

In a meeting in September 1991, the Generic Drugs Advisory Committee (GDAC) concluded that the primary comparison of interest in a bioequivalence study was the ratio rather than the difference between average parameter data from the test and reference formulations. Using log transformation, the general linear statistical model employed in the analysis of bioequivalence data allows inferences about the difference between the two means on the log scale, which can then be re-transformed into inferences about the ratio of the two averages (means or medians) on the original scale. Log transformation thus achieves the general comparison based on the ratio rather than the difference (6).

2. Pharmacokinetic Rationale

Westlake (7,8) observed that a multiplicative model is postulated for pharmacokinetic parameters in bioavailability/bioequivalence studies, i.e., AUC and C_{max} (but not T_{max}). Assuming that elimination of the drug is first order and only occurs from the central compartment, the following equation holds after an extravascular route of administration:

$$AUC_{0-\infty} = FD/CL$$

$$= FD/(VK_e)$$

where F is the fraction absorbed, D is the administered dose, and FD is the amount of drug

absorbed. CL is the clearance of a given subject which is the product of the apparent volume of distribution (V) and the elimination rate constant (K_e).[2]

The use of AUC as a measure of the amount of drug absorbed thus involves a multiplicative term (CL) which might be regarded as a function of the subject. For this reason, Westlake contends that the subject effect is not additive if the data is analyzed on the original scale of measurement.

Logarithmic transformation of the AUC data will bring the CL (VK_e) term into the equation in an additive fashion.

$$\ln AUC_{0-\infty} = \ln F + \ln D - \ln V - \ln K_e$$

Similar arguments were given for C_{max}. The following equation applies for a drug exhibiting one compartmental characteristics:

$$C_{max} = (FD/V) \times e^{-K_e \times T_{max}}$$

where again F, D and V are introduced into the model in a multiplicative manner. However, after logarithmic transformation, the equation becomes

$$\ln C_{max} = \ln F + \ln D - \ln V - K_e T_{max}$$

Log transformation of the C_{max} data also results in the additive treatment of the V term.

3. Statistical Rationale

Logarithmic transformation of the data from bioequivalence studies can be used to circumvent the use of estimates of the reference product average for computation of the confidence interval for the ratio of product averages. This is an

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[2]Note that a more general equation can be written for any multi-compartmental model as

$$AUC_{0-\infty} = FD/(V_{d\beta}\lambda_z)$$

where $V_{d\beta}$ is the volume of distribution relating drug concentration in plasma or blood to the amount of drug in the body during the terminal exponential phase, and λ_z is the terminal slope of the concentration-time curve.

advantage for the cases where a least squares estimate for the reference product mean is not well defined. Standard parametric methods are ill-suited to making inferences about the ratio of two averages, though some valid methods do exist (9). Log transformation changes the problem to one of making inferences about the difference (on the log scale) of two averages, for which the standard methods are well suited.

Many biological data correspond more closely to a log-normal distribution than to a normal distribution. The plasma concentration data including the derived parameters AUC and C_{max} tend to be skewed, and their variances tend to increase with the means. Log transformation is likely to remedy this situation and make the variances independent of the mean. In addition, frequency distributions skewed to the left (with a long tail to the right) are often made more symmetrical by log transformation.

This argument is actually less persuasive than the argument based on the additivity of the statistical model because it is based largely on the between-subject distribution of AUC and C_{max} values. For crossover studies, it is largely the within-subject distribution of values that determines the validity and efficiency of the standard parametric methods of analysis.

Despite the arguments regarding the effect of log transformation on normality of bioequivalence data, the Division of Bioequivalence recognizes that the limited sample size (20-30 subjects) in a bioequivalence study precludes a reliable determination of the underlying normal distribution of the data set either with or without log transformation.

C. General Procedures

Based on the arguments in the preceding section, the Division of Bioequivalence recommends that the pharmacokinetic parameters AUC and C_{max} be log transformed. Firms are not encouraged to test for normality of data distribution after log transformation, nor should they employ normality of data distribution as a justification for carrying out the statistical analysis on the original scale. Robustness of a balanced study to

nonnormality of the data plus use of log transformation will be adequate in most cases.

If a firm believes that the data of a particular bioequivalence study should be statistically analyzed on the original scale rather than the log scale, justification based upon a sound scientific rationale, as well as the statistical methods to be used, ought to be submitted to and reviewed by the Division of Bioequivalence.

D. Presentation of Data

The drug concentration in biological fluid at each sampling time point should be furnished on the original scale for all the subjects who participated in the study. The derived pharmacokinetic parameters should also be furnished on the original scale. The mean, standard deviation, and coefficient of variation for each variable should be computed and tabulated in the final report.

To facilitate bioequivalence comparisons, pharmacokinetic parameters for each individual should be displayed in parallel for the formulations tested. In particular, for AUC and C_{max}, the difference (T-R), ratio (T/R), and log of ratio (log T/R or ln T/R) between the test and reference values should be tabulated side by side for all the subjects. For each subject, the summary tables should indicate in which sequence (test, reference or reference, test) the subject received the product. Firms are encouraged to include histograms showing the frequency distribution of the difference and ln ratio (or log ratio) for the major pharmacokinetic parameters (AUC and C_{max}) in the submission.

In addition to the arithmetic mean for the test and reference products, the geometric means (antilog of the means of the logs), means of the logs, and standard deviations of the logs should be calculated for AUC and C_{max}. All means, including arithmetic mean, geometric mean, and means of the logs, standard deviations, and coefficients of variation are to be included in the report.

It is acceptable to use logarithms to the base 10 rather than natural logarithms. The report must state unambiguously which logarithms were used, and the use must be consistent throughout.

E. Equivalence Criteria

For a broad range of drugs, the Division of Bioequivalence has used a range of 80 to 120% for the ratio of the product averages as the standard equivalence criterion when the study data are analyzed on the original scale. This corresponds to a range of ± 20% for the relative difference between the product averages.

When log-transformed data are used in the analysis of AUC and C_{max}, using a range of 80 to 125% for the ratio of averages has an advantage over the 80 to 120% criterion in that for the analysis of log-transformed data, the probability of concluding equivalence is at a maximum if the ratio of averages is in fact 1.0, i.e., exact equality. For the analysis of log-transformed data with a criterion of 80 to 120%, the maximum probability of concluding equivalence occurs when the ratio of product averages equals approximately 0.98. For this reason, the Division of Bioequivalence has decided to use an equivalence criterion of 80 to 125% for the ratio of the product averages.

The 90% confidence interval for the difference in the means of the log transformed data should be calculated using methods appropriate to the experimental design. The antilogs of the confidence limits so obtained constitute the 90% confidence interval for the ratio of the test and reference product averages.

IV. SEQUENCE EFFECT

A major limitation of a conventional two-treatment, two-period, two-sequence crossover design is the confounding between (i) a true sequence or group effect, (ii) unequal residual or carryover effects, and (iii) treatment-by-period interactions. A true sequence effect (i.e., a difference between the average response for sequence group one and sequence group two) would not bias the determination of bioequivalence. Unequal residual effects, however, would bias this estimate. A treatment-by-period interaction based on an underlying physical basis (i.e., if there were actually something about the periods that caused the difference between the product averages to differ from one period to another), would lead to difficulties in interpreting the estimate of the ratio (difference) in the pharmacokinetic parameters between the test and reference formulations.

Even if there were no true sequence effect, no unequal residual effects, and no period-by-treatment statistical

interaction, approximately ten out of every one hundred standard two-treatment crossover studies would be likely to show an apparent sequence effect, if the testing is carried out at the ten percent level of significance.

If the ANOVA test for the presence of a sequence effect results in statistical significance, the actual cause cannot be determined from the data alone. In some cases, plausible causes might be evaluated by examining demographic or physiological subject data, but this examination is seldom conclusive.

On the basis of these considerations, the Division of Bioequivalence has determined that an *in vivo* standard two-treatment, two-period, two-sequence crossover bioequivalence study showing a statistically significant sequence effect may be acceptable provided:

1. It is a single dose study;

2. It includes only healthy, normal subjects;

3. The drug is not an endogenous entity;

4. More than adequate washout period has been allowed between the two phases of the study, and in the second phase, the predose biological matrix samples do not exhibit any detectable drug level in all subjects; and

5. The study meets all scientific and statistical criteria such as:

    a. It is based upon an acceptable study protocol;

    b. It contains an acceptable validated assay methodology;

    c. The study data are acceptable;

    d. Appropriate statistical analyses of the data are performed; and

    e. Acceptable confidence intervals for the pharmacokinetic parameters are achieved.

Under all other circumstances, the sponsor may be asked to conduct another study. After appropriate review with the Division of Bioequivalence, multiple dose studies and/or studies in patients demonstrating a statistically significant sequence effect may be acceptable provided they meet all other criteria listed above.

V. OUTLIER CONSIDERATION

Subject outliers are defined in bioequivalence studies as subjects having discordant values of one or more pharmacokinetic parameters when compared with other values for the rest of the subjects in a study. Because bioequivalence studies are usually carried out as crossover studies, the most important type of outlier is the within-subject outlier, where one or a few subjects differ notably from the rest of the subjects for the test product response versus the reference product response (e.g., test minus reference difference, test/reference ratio, or the log of the test/reference ratio).

The existence of an outlier could be indicative of the following problems with interchangeability of two formulations:

1. Product failure: a subject obtained an unusually high or low response to one or the other of the products because of a problem with the specific dosage unit(s) administered. Examples include a sustained/modified release dosage form exhibiting dose dumping or a dosage unit whose coating inhibited dissolution.

2. Subpopulation: a subject may be representative of a type of subject, present in the general population in low numbers, for whom the relative bioavailability of the two products is markedly different than it is for the majority of the population, and for whom the two products are not bioequivalent, even though they might be bioequivalent in the majority of the population.

In the case of product failure, it may make a difference whether the unusual response is observed on the test product or the reference product. In the case of a subpopulation, however, even if the unusual response is observed on the reference product, there may still be concern for lack of interchangeability of the two products.

Statistical tests exist for outlier identification. For detection of a single outlier, one important test is based on the absolute value of the Studentized Residual. Out of all the data in the study, the test focuses on the most extreme. Approximate critical values for this test have been published by Lund (10). In principle, however, outliers cannot be dropped from the analysis of the data solely on the basis of a statistical test. Sponsors who have identified one or more outliers should provide scientific evidence or explanations to justify the exclusion of the subject(s) data from statistical analysis.

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EXHIBIT 20

1995

USP 23

NF 18

THE UNITED STATES PHARMACOPEIA

THE NATIONAL FORMULARY

By authority of the United States Pharmacopeial Convention, Inc., meeting at Washington, D.C., March 8–10, 1990. Prepared by the Committee of Revision and published by the Board of Trustees

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UNITED STATES PHARMACOPEIAL CONVENTION, INC.
12601 Twinbrook Parkway, Rockville, MD 20852

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Contents

USP 23

NUTRITIONAL SUPPLEMENTS

NF 18

General Notices and Requirements

Applying to Standards, Tests, Assays, and Other Specifications of the United States Pharmacopeia

Guide to GENERAL NOTICES AND REQUIREMENTS

The *General Notices and Requirements* (hereinafter referred to as the *General Notices*) provide in summary form the basic guidelines for the interpretation and application of the standards, tests, assays, and other specifications of the *United States Pharmacopeia* and obviate the need to repeat throughout the book those requirements that are pertinent in numerous instances.

Where exceptions to the *General Notices* are made, the wording in the individual monograph or general test chapter takes precedence and specifically indicates the directions or the intent. To emphasize that such exceptions do exist, the *General Notices* employ where indicated a qualifying expression such as "unless otherwise specified." Thus, it is understood that the specific wording of standards, tests, assays, and other specifications is binding wherever deviations from the *General Notices* exist. By the same token, where no language is given specifically to the contrary, the *General Notices* apply.

TITLE

The full title of this book, including its supplements, is The Pharmacopeia of the United States of America, Twenty-third Revision. This title may be abbreviated to *United States Pharmacopeia*, Twenty-third Revision, or to *USP 23*. The *United States Pharmacopeia*, Twenty-third Revision, supersedes all earlier revisions. Where the term USP is used, without further qualification, during the period in which this Pharmacopeia is official, it refers only to *USP 23* and any supplement(s) thereto.

"OFFICIAL" AND "OFFICIAL ARTICLES"

The word "official," as used in this Pharmacopeia or with reference hereto, is synonymous with "Pharmacopeial," with "USP," and with "compendial."

The designation USP in conjunction with the official title on the label of an article means that the article purports to comply with USP standards; such specific designation on the label does not constitute a representation, endorsement, or incorporation by the manufacturer's labeling of the informational material contained in the USP monograph, nor does it constitute assurance by USP that the article is known to comply with USP standards. The standards apply equally to articles bearing the official titles or names derived by transposition of the definitive words of official titles or transposition in the order of the names of two or more active ingredients in official titles, whether or not the added designation "USP" is used. Names considered to be synonyms of the official titles may not be used for official titles.

Where an article differs from the standards of strength, quality, and purity, as determined by the application of the assays and tests set forth for it in the Pharmacopeia, its difference shall be plainly stated on its label. Where an article fails to comply in identity with the identity prescribed in the USP, or contains an added substance that interferes with the prescribed assays and tests, such article shall be designated by a name that is clearly distinguishing and differentiating from any name recognized in the Pharmacopeia.

Articles listed herein are official and the standards set forth in the monographs apply to them only when the articles are intended or labeled for use as drugs, as nutritional supplements, or as medical devices and when bought, sold, or dispensed for these purposes or when labeled as conforming to this Pharmacopeia.

An article is deemed to be recognized in this Pharmacopeia when a monograph for the article is published in it, including its supplements, addenda, or other interim revisions, and an official date is generally or specifically assigned to it.

The following terminology is used for distinguishing the articles for which monographs are provided: an *official substance* is an active drug entity, a recognized nutrient, or a pharmaceutic ingredient (see also *NF 18*) or a component of a finished device for which the monograph title includes no indication of the nature of the finished form; an *official preparation* is a *drug product*, a *nutritional supplement* or a *finished device*. It is the finished or partially finished (e.g., as in the case of a sterile solid to be constituted into a solution for administration) preparation or product of one or more official substances formulated for use on or for the patient or consumer; an *article* is an item for which a monograph is provided, whether an official substance or an official preparation.

Nutritional Supplements—The designation of an official preparation containing recognized nutrients as "USP" or the use of the designation "USP" in conjunction with the title of such nutritional supplement preparation may be made only if the article contains two or more of the recognized nutrients and the preparation meets the applicable requirements contained in the individual Class Monograph and General Chapters. Any additional ingredient in such article that is not recognized in the pharmacopeia and for which nutritional value is claimed, shall not be represented nor imply that it is of USP quality. A recognized by USP. If a preparation does not comply with applicable requirements but contains nutrients that are recognized in the USP, the article may not designate the individual nutrients as complying with USP standards or being of USP quality without designating on the label that the article itself does not comply with USP standards.

ATOMIC WEIGHTS AND CHEMICAL FORMULAS

The atomic weights used in computing molecular weights and the factors in the assays and elsewhere are those recommended in 1991 by the IUPAC Commission on Atomic Weights and Isotopic Abundances. Chemical formulas, other than those in the Definitions, tests, and assays, are given for purposes of information and calculation. The format within a given monograph is such that after the official title the primarily informational portions of the text are

pear first, followed by the text comprising requirements, the latter section of the monograph being introduced by a boldface double-arrow symbol ». (Graphic formulas and chemical nomenclature provided as information in the individual monographs are discussed in the *Preface*.)

ABBREVIATIONS

The term RS refers to a USP Reference Standard as stated under *Reference Standards* in these *General Notices* (see also *USP Reference Standards* ⟨11⟩).

The terms CS and TS refer to Colorimetric Solution and Test Solution, respectively (see under *Reagents, Indicators, and Solutions*). The term VS refers to Volumetric Solution as stated under *Solutions* in the *General Notices*.

The term *PF* refers to *Pharmacopeial Forum*, the journal of standards development and official compendia revision (see *Pharmacopeial Forum* in these *General Notices*).

Abbreviations for the names of many institutions, organizations, and publications are used for convenience throughout *USP* and *NF*. An alphabetized tabulation follows.

Abbreviation	Institution, Organization, or Publication
AAMI	Association for the Advancement of Medical Instrumentation
ACS	American Chemical Society
ANSI	American National Standards Institute
AOAC	AOAC International (formerly Association of Official Analytical Chemists)
ASTM	American Society for Testing and Materials
ATCC	American Type Culture Collection
CAS	Chemical Abstracts Service
CFR	U.S. Code of Federal Regulations
EPA	U.S. Environmental Protection Agency
FCC	Food Chemicals Codex
FDA	U.S. Food and Drug Administration
HIMA	Health Industry Manufacturers Association
ISO	International Standards Organization
IUPAC	International Union of Pure and Applied Chemistry
NBS	National Bureau of Standards
NIST	National Institute of Standards and Technology (formerly NBS)
USAN	United States Adopted Names
WHO	World Health Organization

Abbreviated Statements in Monographs—Incomplete sentences are employed in various portions of the monographs for directness and brevity. Where the limit tests are so abbreviated, it is to be understood that the chapter numbers (shown in angle brackets) designate the respective procedures to be followed, and that the values specified after the colon are the required limits.

SIGNIFICANT FIGURES AND TOLERANCES

Where limits are expressed numerically herein, the upper and lower limits of a range include the two values themselves and all intermediate values, but no values outside the limits. The limits expressed in monograph definitions and tests, regardless of whether the values are expressed as percentages or as absolute numbers, are considered significant to the last digit shown.

Equivalence Statements in Titrimetric Procedures—The directions for titrimetric procedures conclude with a statement of the weight of the analyte that is equivalent to each mL of the standardized titrant. In such an equivalence statement, it is to be understood that the number of significant figures in the concentration of the titrant corresponds to the number of significant figures in the weight of the analyte. Blank corrections are to be made for all titrimetric assays where appropriate (see *Titrimetry* ⟨541⟩).

Tolerances—The limits specified in the monographs for Pharmacopeial articles are established with a view to the use of these articles as drugs, except where it is indicated otherwise. The use of the molecular formula for the active ingredient(s) named in defining the required strength of a Pharmacopeial article is intended to designate the chemical entity or entities, as given in the complete chemical name of the article, having absolute (100 percent) purity.

A dosage form shall be formulated with the intent to provide 100 percent of the quantity of each ingredient declared on the label. Where the content of an ingredient is known to decrease with time, an amount in excess of that declared on the label may be introduced into the dosage form at the time of manufacture to assure compliance with the content requirements of the monograph throughout the expiration period. The tolerances and limits stated in the definitions in the monographs for Pharmacopeial articles allow for such overages and for analytical error, for unavoidable variations in manufacturing and compounding, and for deterioration to an extent considered acceptable under practical conditions.

The specified tolerances are based upon such attributes of quality as might be expected to characterize an article produced from suitable raw materials under recognized principles of good manufacturing practice.

The existence of compendial limits or tolerances does not constitute a basis for a claim that an official substance that more nearly approaches 100 percent purity "exceeds" the Pharmacopeial quality. Similarly, the fact that an article has been prepared to closer tolerances than those specified in the monograph does not constitute a basis for a claim that the article "exceeds" the Pharmacopeial requirements.

Interpretation of Requirements—Analytical results observed in the laboratory (or calculated from experimental measurements) are compared with stated limits to determine whether there is conformance with compendial assay or test requirements. The observed or calculated values usually will contain more significant figures than there are in the stated limit, and an observed or calculated result is to be rounded off to the number of places that is in agreement with the limit expression by the following pro-

cedure. [NOTE—Limits, which are fixed numbers, are not rounded off.]

When rounding off is required; consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than 5, it is eliminated and the preceding digit is unchanged. If this digit is greater than 5, it is eliminated and the preceding digit is increased by one. If this digit equals 5, the 5 is eliminated and the preceding digit is increased by one.

Illustration of Rounding Numerical Values for Comparison with Requirements

Compendial Requirement	Unrounded Value	Rounded Result	Conforms
Assay limit ≥98.0%	97.96%	98.0%	Yes
	97.92%	97.9%	No
	97.95%	98.0%	Yes
Assay limit ≤101.5%	101.55%	101.6%	No
	101.46%	101.5%	Yes
	101.45%	101.5%	Yes
Limit test ≤0.02%	0.025%	0.03%	No
	0.015%	0.02%	Yes
	0.027%	0.03%	No
Limit test ≤3 ppm	0.00035%	0.0004%	No
	0.00025%	0.0003%	Yes
	0.00028%	0.0003%	Yes

GENERAL CHAPTERS

Each general chapter is assigned a number that appears in brackets adjacent to the chapter name (e.g., ⟨601⟩ *Aerosols*). General chapters that include general *requirements* for tests and assays are numbered from ⟨1⟩ to ⟨999⟩, chapters that are *informational* are numbered from ⟨1000⟩ to ⟨1999⟩, and chapters pertaining to *nutritional supplements* are numbered above ⟨2000⟩.

The use of the general chapter numbers is encouraged for the identification and rapid access to general tests and information. It is especially helpful where monograph section headings and chapter names are not the same (e.g., *Ultraviolet absorption* ⟨197U⟩ in a monograph refers to method ⟨197U⟩ under general tests chapter ⟨197⟩ *Spectrophotometric Identification Tests; Specific rotation* ⟨781S⟩ in a monograph refers to method ⟨781S⟩ under general tests chapter ⟨781⟩ *Optical Rotation;* and *Calcium* ⟨191⟩ in a monograph refers to the tests for *Calcium* under general tests chapter ⟨191⟩ *Identification Tests—General*).

PHARMACOPEIAL FORUM

Pharmacopeial Forum (*PF*) is the USP journal of standards development and official compendia revision. *Pharmacopeial Forum* is the working document of the USP Committee of Revision. It is intended to provide public portions of communications within the General Committee of Revision and public notice of proposed new and revised standards of the *USP* and *NF* and to afford opportunity for comment thereon. The organization of *PF* includes, but is not limited to, the following sections. Subsections occur where needed for Drugs and Pharmaceutic Ingredients and for Nutritional Supplements.

Pharmacopeial Previews—Possible revisions that are considered to be in a preliminary stage of development.

In-process Revision—New or revised monographs or chapters that are proposed for adoption as official USP or NF standards.

Stimuli to the Revision Process—Reports, statements, articles, or commentaries relating to compendial issues.

Nomenclature—Articles and announcements relevant to compendial nomenclature issues and listings of proposed and new United States Adopted Names (USAN) and International Nonproprietary Names (INN).

Interim Revision Announcement (if present)—Official revisions and their effective dates, announcement of the availability of new USP Reference Standards, and announcement of assays or tests that are held in abeyance pending availability of required USP Reference Standards.

Official Reference Standards—Catalog of current lots of USP Reference Standards with ordering information and names and addresses of worldwide suppliers.

REAGENT STANDARDS

The proper conduct of the Pharmacopeial tests and assays and the reliability of the results depend, in part, upon the quality of the reagents used in the performance of the procedures. Unless otherwise specified, reagents are to be used that conform to the specifications set forth in the current edition of *Reagent Chemicals* published by the American Chemical Society. Where such ACS reagent specifications are not available or where for various reasons the required purity differs, compendial specifications for reagents of acceptable quality are provided. (See *Reagents, Indicators, and Solutions.*) Listing of these reagents, including the indicators and solutions employed as reagents, in no way implies that they have therapeutic utility; furthermore, any reference to USP or NF in their labeling shall include also the term "reagent" or "reagent grade."

USP REFERENCE STANDARDS

USP Reference Standards are authentic specimens that have been approved by the USP Reference Standards Committee as suitable for use as comparison standards in USP or NF tests and assays. (See *USP Reference Standards* ⟨11⟩.) Currently official lots of USP Reference Standards are published in *Pharmacopeial Forum.*

Where a USP Reference Standard is referred to in a monograph or chapter, the words "Reference Standard" are abbreviated to "RS" (see *USP Reference Standards* ⟨11⟩).

Where a test or an assay calls for the use of a compendial article rather than for a USP Reference Standard as a material standard of reference, a substance meeting all of the compendial monograph requirements for that article is to be used.

The requirements for any new USP or NF standards, tests, or assays for which a new USP Reference Standard is specified are not in effect until the specified USP Reference Standard is available. The availability of new USP Reference Standards and the official dates of the USP or NF standards, tests, or assays requiring their use are announced via *Supplements* or *Interim Revision Announcements*.

UNITS OF POTENCY

For substances that cannot be completely characterized by chemical and physical means, it may be necessary to express quantities of activity in biological units of potency, each defined by an authoritative, designated reference standard.

Units of biological potency defined by the World Health Organization (WHO) for International Biological Standards and International Biological Reference Preparations are termed International Units (IU). Units defined by USP Reference Standards are USP Units, and the individual monographs refer to these. Unless otherwise indicated, USP Units are equivalent to the corresponding International Units, where such exist. Such equivalence is usually established on the basis solely of the compendial assay for the substance.

For antibiotics (see *Antibiotics—Microbial Assays* ⟨81⟩), USP Units are defined by the corresponding USP Reference Standards in terms of the units of activity established by the FDA. Each unit is established through the corresponding antibiotic master standard, which in many instances is the basis also for the definition of the WHO International Unit. For most antibiotics, however, biological units of potency are not necessary, and their activity is expressed in metric units (micrograms or milligrams) in terms of the chemically defined substances described in the individual monographs.

For biological products, whether or not International Units or USP Units do exist (see *Biologics* ⟨1041⟩), units of potency are defined by the corresponding US Standard established by the FDA.

INGREDIENTS AND PROCESSES

Official preparations are prepared from ingredients that meet the requirements of the compendial monographs for those individual ingredients for which monographs are provided (see also *NF 18*).

Official substances are prepared according to recognized principles of good manufacturing practice and from ingredients complying with specifications designed to assure that the resultant substances meet the requirements of the compendial monographs (see also *Foreign Substances and Impurities* under *Tests and Assays*).

Preparations for which a complete composition is given in this Pharmacopeia, unless specifically exempted herein or in the individual monograph, are to contain only the ingredients named in the formulas. However, there may be deviation from the specified processes or methods of compounding, though not from the ingredients or proportions thereof, provided the finished preparation conforms to the relevant standards laid down herein and to preparations produced by following the specified process.

Where a monograph on a preparation calls for an ingredient in an amount expressed on the dried basis, the ingredient need not be dried prior to use if due allowance is made for the water or other volatile substances present in the quantity taken.

Unless specifically exempted elsewhere in this Pharmacopeia, the identity, strength, quality, and purity of an official article are determined by the definition, physical properties, tests, assays, and other specifications relating to the article, whether incorporated in the monograph itself, in the *General Notices*, or in the section *General Chapters*.

Water—Water used as an ingredient of official preparations meets the requirements for *Purified Water*, for *Water for Injection*, or for one of the sterile forms of water covered by a monograph in this Pharmacopeia.

Potable water meeting the requirements for drinking water as set forth in the regulations of the federal Environmental Protection Agency may be used in the preparation of official substances.

Alcohol—All statements of percentages of alcohol, such as under the heading *Alcohol content* refer to percentage, by volume, of C_2H_5OH at 15.56°. Where reference is made to "C_2H_5OH," the chemical entity possessing absolute (100 percent) strength is intended.

Alcohol—Where "alcohol" is called for in formulas, tests, and assays, the monograph article *Alcohol* is to be used.

Dehydrated Alcohol—Where "dehydrated alcohol" (absolute alcohol) is called for in tests and assays, the monograph article *Dehydrated Alcohol* is to be used.

Denatured Alcohol—Specially denatured alcohol formulas are available for use in accordance with federal statutes and regulations of the Internal Revenue Service. A suitable formula of specially denatured alcohol may be substituted for Alcohol in the manufacture of Pharmacopeial preparations intended for internal or topical use, provided that the denaturant is volatile and does not remain in the finished product. A finished product that is intended for topical application to the skin may contain specially denatured alcohol, provided that the denaturant is either a normal ingredient or a permissible added substance; in either case the denaturant must be identified on the label of the topical preparation. Where a process is

given in the individual monograph, the preparation so made must be identical with that prepared by the given process.

Added Substances—An official substance, as distinguished from an official preparation, contains no added substances except where specifically permitted in the individual monograph. Where such addition is permitted, the label indicates the name(s) and amount(s) of any added substance(s).

Unless otherwise specified in the individual monograph, or elsewhere in the *General Notices*, suitable substances such as antimicrobial agents, bases, carriers, coatings, colors, flavors, preservatives, stabilizers, and vehicles may be added to an official preparation to enhance its stability, usefulness, or elegance or to facilitate its preparation. Such substances are regarded as unsuitable and are prohibited unless (a) they are harmless in the amounts used, (b) they do not exceed the minimum quantity required to provide their intended effect, (c) their presence does not impair the bioavailability or the therapeutic efficacy or safety of the official preparation, and (d) they do not interfere with the assays and tests prescribed for determining compliance with the Pharmacopeial standards.

Nutritional Supplements—Unless otherwise specified in the individual monograph, or elsewhere in the *General Notices*, consistent with applicable regulatory requirements, suitable added substances such as bases, carriers, coatings, colors, flavors, preservatives, and stabilizers may be added to a nutritional supplement preparation to enhance its stability, usefulness, or elegance, or to facilitate its preparation. Such added substances shall be regarded suitable and shall be permitted unless they interfere with the assays and tests prescribed for determining compliance with Pharmacopeial standards.

Additional Ingredients—Additional ingredients, including excipients, may be added to nutritional supplement preparations containing *recognized nutrients*, consistent with applicable regulatory requirements, provided that (a) they do not interfere with the assays and tests prescribed for determining compliance with Pharmacopeial standards, and (b) that such additional ingredients are listed separately on the label from those ingredients recognized in the definition of the USP article.

Inert Headspace Gases—The air in a container of an article for parenteral use may be evacuated or be replaced by carbon dioxide, helium, or nitrogen, or by a mixture of these gases, which fact need not be declared in the labeling.

Colors—Added substances employed solely to impart color may be incorporated into official preparations, except those intended for parenteral or ophthalmic use, in accordance with the regulations pertaining to the use of colors issued by the FDA provided such added substances are otherwise appropriate in all respects. (See also *Added Substances* under *Injections* ⟨1⟩.)

Ointments and Suppositories—In the preparation of ointments and suppositories, the proportions of the substances constituting the base may be varied to maintain a suitable consistency under different climatic conditions, provided the concentrations of active ingredients are not varied.

TESTS AND ASSAYS

Apparatus—A specification for a definite size or type of container or apparatus in a test or assay is given solely as a recommendation. Where volumetric flasks or other exact measuring, weighing, or sorting devices are specified, this or other equipment of at least equivalent accuracy shall be employed. (See also *Thermometers* ⟨21⟩, *Volumetric Apparatus* ⟨31⟩, and *Weights and Balances* ⟨41⟩). Where low-actinic or light-resistant containers are specified, clear containers that have been rendered opaque by application of a suitable coating or wrapping may be used.

Where an instrument for physical measurement, such as a spectrophotometer, is specified in a test or assay by its distinctive name, another instrument of equivalent or greater sensitivity and accuracy may be used. In order to obtain solutions having concentrations that are adaptable to the working range of the instrument being used, solutions of proportionately higher or lower concentrations may be prepared according to the solvents and proportions thereof that are specified for the procedure.

Where a particular brand or source of a material, instrument, or piece of equipment, or the name and address of a manufacturer or distributor, is mentioned (ordinarily in a footnote), this identification is furnished solely for informational purposes as a matter of convenience, without implication of approval, endorsement, or certification. Items capable of equal or better performance may be used if these characteristics have been validated.

Where the use of a centrifuge is indicated, unless otherwise specified, the directions are predicated upon the use of apparatus having an effective radius of about 20 cm (8 inches) and driven at a speed sufficient to clarify the supernatant layer within 15 minutes.

Unless otherwise specified, for chromatographic tubes and columns the diameter specified refers to internal diameter (ID); for other types of tubes and tubing the diameter specified refers to outside diameter (OD).

Steam Bath—Where the use of a steam bath is directed, exposure to actively flowing steam or to another form of regulated heat, corresponding in temperature to that of flowing steam, may be used.

Water Bath—Where the use of a water bath is directed without qualification with respect to temperature, a bath of vigorously boiling water is intended.

Foreign Substances and Impurities—Tests for the presence of foreign substances and impurities are provided to limit such substances to amounts that are unobjectionable under conditions in which the article is customarily employed (see also *Impurities in Official Articles* ⟨1086⟩).

While one of the primary objectives of the Pharmacopeia is to assure the user of official articles of their identity, strength, quality, and purity, it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present, including microbial contamination. These may arise from a change in the source of material or from a change in the processing, or may be introduced from extraneous sources. Tests suitable for detecting such occurrences, the presence of which is inconsistent with applicable manufacturing practice or good pharmaceutical practice, should be employed in addition to the tests provided in the individual monograph.

Procedures—Assay and test procedures are provided for determining compliance with the Pharmacopeial standards of identity, strength, quality, and purity.

In performing the assay or test procedures in this Pharmacopeia, it is expected that safe laboratory practices will be followed. This includes the utilization of precautionary measures, protective equipment, and work practices consistent with the chemicals and procedures utilized. Prior to undertaking any assay or procedure described in this Pharmacopeia, the individual should be aware of the hazards associated with the chemicals and the procedures and means of protecting against them. This Pharmacopeia is not designed to describe such hazards or protective measures.

Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all of the requirements in the monograph defining it. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing *process validation* studies and from *in-process controls* may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards.

Automated procedures employing the same basic chemistry as those assay and test procedures given in the monograph are recognized as being equivalent in their suitability for determining compliance. Conversely, where an automated procedure is given in the monograph, manual procedures employing the same basic chemistry are recognized as being equivalent in their suitability for determining compliance. Compliance may be determined also by the use of alternative methods, chosen for advantages in accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction or in other special circumstances. Such alternative or automated procedures or methods shall be validated. However, Pharmacopeial standards and procedures are interrelated; therefore, where a difference appears or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.

In the performance of assay or test procedures, not less than the specified number of dosage units should be taken for analysis. Proportionately larger or smaller quantities than the specified weights and volumes of assay or test substances and Reference Standards may be taken, provided the measurement is made with at least equivalent accuracy and provided that any subsequent steps, such as dilutions, are adjusted accordingly to yield concentrations equivalent to those specified and are made in such manner as to provide at least equivalent accuracy.

Where it is directed in an assay or a test that a certain quantity of substance or a counted number of dosage units is to be examined, the specified quantity or number is a minimal figure (the singlet determination) chosen only for convenience of analytical manipulation; it is not intended to restrict the total quantity of substance or number of units that may be subjected to the assay or test or that should be tested in accordance with good manufacturing practices.

Where it is directed in the assay of Tablets to "weigh and finely powder not less than" a given number, usually 20, of the Tablets, it is intended that a counted number of Tablets shall be weighed and reduced to a powder. The portion of the powdered tablets taken for assay is representative of the whole Tablets and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Tablet by multiplying this result by the average Tablet weight and dividing by the weight of the portion taken for the assay.

Similarly, where it is directed in the assay of Capsules to remove, as completely as possible, the contents of not less than a given number, usually 20, of the Capsules, it is intended that a counted number of Capsules should be carefully opened and the contents quantitatively removed, combined, mixed, and weighed accurately. The portion of mixed Capsules contents taken for the assay is representative of the contents of the Capsules and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Capsule by multiplying this result by the average weight of Capsule content and dividing by the weight of the portion taken for the assay.

Where the definition in a monograph states the tolerances as being "calculated on the dried (or anhydrous or ignited) basis," the directions for drying or igniting the sample prior to assaying are generally omitted from the *Assay* procedure. Assay and test procedures may be performed on the undried or unignited substance and the results calculated on the dried, anhydrous, or ignited basis, provided a test for *Loss on drying*, or *Water*, or *Loss on ignition*, respectively, is given in the monograph. Where the presence of moisture or other volatile material may interfere with the procedure, previous drying of the substance is specified in the individual monograph and is obligatory.

Throughout a monograph that includes a test for *Loss on drying* or *Water*, the expression "previously dried" without qualification signifies that the substance is to be dried as directed under *Loss on drying* or *Water* (gravimetric determination).

Unless otherwise directed in the test or assay in the individual monograph or in a general chapter, USP Reference Standards are to be dried before use, or used without prior drying, specifically in accordance with the instructions given in the chapter *USP Reference Standards* ⟨11⟩, and on the label of the Reference Standard. Where the label instructions differ in detail from those in the chapter, the label text is determinative.

In stating the appropriate quantities to be taken for assays and tests, the use of the word "about" indicates a quantity within 10% of the specified weight or volume. However, the weight or volume taken is accurately determined and the calculated result is based upon the exact amount taken. The same tolerance applies to specified dimensions.

Where the use of a pipet is directed for measuring a specimen or an aliquot in conducting a test or an assay, the pipet conforms to the standards set forth under *Volumetric Apparatus* ⟨31⟩, and is to be used in such manner that the error does not exceed the limit stated for a pipet of its size. Where a pipet is specified, a suitable buret, conforming to the standards set forth under *Volumetric Apparatus* ⟨31⟩, may be substituted. Where a "to contain" pipet is specified, a suitable volumetric flask may be substituted.

Expressions such as "25.0 mL" and "25.0 mg," used with respect to volumetric or gravimetric measurements, indicate that the quantity is to be "accurately measured" or "accurately weighed" within the limits stated under *Volumetric Apparatus* ⟨31⟩ or under *Weights and Balances* ⟨41⟩.

The term "transfer" is used generally to specify a quantitative manipulation.

The term "concomitantly," used in such expressions as "concomitantly determine" or "concomitantly measured," in directions for assays and tests, is intended to denote that the determinations or measurements are to be performed in immediate succession. See also *Use of Reference Standards* under *Spectrophotometry and Light-scattering* ⟨851⟩.

Blank Determination—Where it is directed that "any necessary correction" be made by a blank determination, the determination is to be conducted using the same quantities of the same reagents treated in the same manner as the solution or mixture containing the portion of the substance under assay or test, but with the substance itself omitted.

Desiccator—The expression "in a desiccator" specifies the use of a tightly closed container of suitable size and design that maintains an atmosphere of low moisture content by means of silica gel or other suitable desiccant.

A "vacuum desiccator" is one that maintains the low-moisture atmosphere at a reduced pressure of not more than 20 mm of mercury or at the pressure designated in the individual monograph.

Dilution—Where it is directed that a solution be diluted "quantitatively and stepwise," an accurately measured portion is to be diluted by adding water or other solvent, in the proportion indicated, in one or more steps. The choice of apparatus to be used should take into account the relatively larger errors generally associated with using small-volume volumetric apparatus (see *Volumetric Apparatus* ⟨31⟩).

Drying to Constant Weight—The specification "dried to constant weight" means that the drying shall be continued until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional hour of drying.

Filtration—Where it is directed to "filter," without further qualification, the intent is that the liquid be filtered through suitable filter paper or equivalent device until the filtrate is clear.

Identification Tests—The Pharmacopeial tests headed *Identification* are provided as an aid in verifying the identity of articles as they are purported to be, such as those taken from labeled containers. Such tests, however specific, are not necessarily sufficient to establish proof of identity; but failure of an article taken from a labeled container to meet the requirements of a prescribed identification test indicates that the article may be mislabeled. Other tests and specifications in the monograph often contribute to establishing or confirming the identity of the article under examination.

Ignition to Constant Weight—The specification "ignite to constant weight" means that the ignition shall be continued, at 800 ± 25° unless otherwise indicated, until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional 15-minute ignition period.

Indicators—Where the use of a test solution ("TS") as an indicator is specified in a test or an assay, approximately 0.2 mL, or 3 drops, of the solution shall be added, unless otherwise directed.

Logarithms—Logarithms used in the assays are to the base 10.

Microbial Strains—Where a microbial strain is cited and identified by its ATCC catalog number, the specified strain shall be used directly or, if subcultured, shall be used not more than five passages removed from the original strain.

Negligible—This term indicates a quantity not exceeding 0.50 mg.

Odor—Terms such as "odorless," "practically odorless," "a faint characteristic odor," or variations thereof, apply to examination, after exposure to the air for 15 minutes, of either a freshly opened package of the article (for packages containing not more than 25 g) or (for larger packages) of a portion of about 25 g of the article that has been removed from its package to an open evaporating dish of about 100-mL capacity. An odor designation is descriptive only

and is not to be regarded as a standard of purity for a particular lot of an article.

Pressure Measurements—The term "mm of mercury" used with respect to measurements of blood pressure, pressure within an apparatus, or atmospheric pressure refers to the use of a suitable manometer or barometer calibrated in terms of the pressure exerted by a column of mercury of the stated height.

Solutions—Unless otherwise specified in the individual monograph, all solutions called for in tests and assays are prepared with *Purified Water*.

An expression such as "(1 in 10)" means that 1 part *by volume* of a liquid is to be diluted with, or 1 part *by weight* of a solid is to be dissolved in, sufficient of the diluent or solvent to make the volume of the finished solution 10 parts *by volume*.

An expression such as "(20:5:2)" means that the respective numbers of parts, by volume, of the designated liquids are to be mixed, unless otherwise indicated.

The notation "VS" after a specified volumetric solution indicates that such solution is standardized in accordance with directions given in the individual monograph or under *Volumetric Solutions* in the section *Reagents, Indicators, and Solutions*, and is thus differentiated from solutions of approximate normality or molarity.

Where a standardized solution of a specific concentration is called for in a test or an assay, a solution of other normality or molarity may be used, provided allowance is made for the difference in concentration and provided the error of measurement is not increased thereby.

Specific Gravity—Unless otherwise stated, the specific gravity basis is 25°/25°, i.e., the ratio of the weight of a substance in air at 25° to the weight of an equal volume of water at the same temperature.

Temperatures—Unless otherwise specified, all temperatures in this Pharmacopeia are expressed in centigrade (Celsius) degrees, and all measurements are made at 25°. See *Storage Temperature* under *Preservation, Packaging, Storage, and Labeling* for other definitions.

Time Limit—In the conduct of tests and assays, 5 minutes shall be allowed for the reaction to take place unless otherwise specified.

Vacuum—The term "in vacuum" denotes exposure to a pressure of less than 20 mm of mercury unless otherwise indicated.

Where drying in vacuum over a desiccant is directed in the individual monograph, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus, is to be used.

Water—Where water is called for in tests and assays, *Purified Water* is to be used unless otherwise specified. For special kinds of water such as "carbon dioxide–free water," see the introduction to the section *Reagents, Indicators, and Solutions*. For *High-purity Water* see *Containers* ⟨661⟩.

Water and *Loss on Drying*—Where the water of hydration or adsorbed water of a Pharmacopeial article is determined by the titrimetric method, the test is generally given under the heading *Water*. Monograph limits expressed as a percentage are figured on a weight/weight basis unless otherwise specified. Where the determination is made by drying under specified conditions, the test is generally given under the heading *Loss on drying*. However, *Loss on drying* is most often given as the heading where the loss in weight is known to represent residual volatile constituents including organic solvents as well as water.

Test Results, Statistics, and Standards—Interpretation of results from official tests and assays requires an understanding of the nature and style of compendial standards, in addition to an understanding of the scientific and mathematical aspects of laboratory analysis and quality assurance for analytical laboratories.

Confusion of compendial standards with release tests and with statistical sampling plans occasionally occurs. Compendial standards define what is an acceptable article and give test procedures that demonstrate that the article is in compliance. These standards apply at any time in the life of the article from production to consumption. The manufacturer's release specifications, and compliance with good manufacturing practices generally, are developed and followed to assure that the article will indeed comply with compendial standards until its expiration date, when stored as directed. Thus, when tested from the viewpoint of commercial or regulatory compliance, any specimen tested as directed in the monograph for that article shall comply (see *Test and Assays* under *General Notices*).

Tests and assays in this Pharmacopeia prescribe operation on a single specimen, that is, the singlet determination, which is the minimum sample on which the attributes of a compendial article should be measured. Some tests, such as those for *Dissolution* and *Uniformity of dosage units*, require multiple dosage units in conjunction with a decision scheme. These tests, albeit using a number of dosage units, are in fact the singlet determinations of those particular attributes of the specimen. These procedures should not be confused with statistical sampling plans. The compendial procedures demonstrate compliance of the attributes of an article with compendial standards for a specimen (of one or more dosage units) that is subjected to analysis. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations are neither specified nor proscribed by the compendia; such decisions are dependent on the objectives of the testing. Commercial or regulatory compliance testing, or manufacturer's release testing, may or may not require examination of additional specimens, in accordance with predetermined guidelines or sampling strategies. Treatments of data handling are available from organizations such as ISO, IUPAC, and AOAC.

Description—Information on the "description" pertaining to an article, which is relatively general in

nature, is provided in the reference table *Description and Relative Solubility of USP and NF Articles* in this Pharmacopeia for those who use, prepare, and dispense drugs and/or related articles, solely to indicate properties of an article complying with monograph standards. The properties are not in themselves standards or tests for purity even though they may indirectly assist in the preliminary evaluation of an article.

Solubility—The statements concerning solubilities given in the reference table *Description and Relative Solubility of USP and NF Articles* for Pharmacopeial articles are not standards or tests for purity but are provided primarily as information for those who use, prepare, and dispense drugs and/or related articles. Only where a quantitative solubility test is given, and is designated as such, is it a test for purity.

The approximate solubilities of Pharmacopeial substances are indicated by the descriptive terms in the accompanying table.

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 and over

Soluble Pharmacopeial articles, when brought into solution, may show traces of physical impurities, such as minute fragments of filter paper, fibers, and other particulate matter, unless limited or excluded by definite tests or other specifications in the individual monographs.

PRESCRIBING AND DISPENSING

Prescriptions for compendial articles shall be written to state the quantity and/or strength desired in metric units unless otherwise indicated in the individual monograph (see also *Units of Potency* in these *General Notices*). If an amount is prescribed by any other system of measurement, only an amount that is the metric equivalent of the prescribed amount shall be dispensed.

PRESERVATION, PACKAGING, STORAGE, AND LABELING

Containers—The *container* is that which holds the article and is or may be in direct contact with the article. The *immediate container* is that which is in direct contact with the article at all times. The *closure* is a part of the container.

Prior to its being filled, the container should be clean. Special precautions and cleaning procedures may be necessary to ensure that each container is clean and that extraneous matter is not introduced into or onto the article.

The container does not interact physically or chemically with the article placed in it so as to alter the strength, quality, or purity of the article beyond the official requirements.

The Pharmacopeial requirements for the use of specified containers apply also to articles as packaged by the pharmacist or other dispenser, unless otherwise indicated in the individual monograph.

Tamper-resistant Packaging—The container or individual carton of a sterile article intended for ophthalmic or otic use, except where extemporaneously compounded for immediate dispensing on prescription, shall be so sealed that the contents cannot be used without obvious destruction of the seal.

Articles intended for sale without prescription are also required to comply with the tamper-resistant packaging and labeling requirements of the FDA where applicable.

Preferably, the immediate container and/or the outer container or protective packaging utilized by a manufacturer or distributor for all dosage forms that are not specifically exempt is designed so as to show evidence of any tampering with the contents.

Light-resistant Container (see *Light Transmission* under *Containers* ⟨661⟩)—A light-resistant container protects the contents from the effects of light by virtue of the specific properties of the material of which it is composed, including any coating applied to it. Alternatively, a clear and colorless or a translucent container may be made light-resistant by means of an opaque covering, in which case the label of the container bears a statement that the opaque covering is needed until the contents are to be used or administered. Where it is directed to "protect from light" in an individual monograph, preservation in a light-resistant container is intended.

Where an article is required to be packaged in a light-resistant container, and if the container is made light-resistant by means of an opaque covering, a single-use, unit-dose container or mnemonic pack for dispensing may not be removed from the outer opaque covering prior to dispensing.

Well-closed Container—A well-closed container protects the contents from extraneous solids and from loss of the article under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Tight Container—A tight container protects the contents from contamination by extraneous liquids, solids, or vapors, from loss of the article, and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution, and is capable of tight re-closure. Where a tight container is specified, it may be replaced by a hermetic container for a single dose of an article.

A gas cylinder is a metallic container designed to hold a gas under pressure. As a safety measure, for carbon dioxide, cyclopropane, helium, nitrous oxide,

and oxygen, the Pin-index Safety System of matched fittings is recommended for cylinders of Size E or smaller.

NOTE—Where packaging and storage in a *tight container* or a *well-closed container* is specified in the individual monograph, the container utilized for an article when dispensed on prescription meets the requirements under *Containers—Permeation* ⟨671⟩.

Hermetic Container—A hermetic container is impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Single-unit Container—A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show evidence of any tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity and/or strength, name of the manufacturer, lot number, and expiration date of the article.

Single-dose Container (see also *Containers for Injections* under *Injections* ⟨1⟩)—A single-dose container is a single-unit container for articles intended for parenteral administration only. A single-dose container is labeled as such. Examples of single-dose containers include pre-filled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled.

Unit-dose Container—A unit-dose container is a single-unit container for articles intended for administration by other than the parenteral route as a single dose, direct from the container.

Multiple-unit Container—A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

Multiple-dose Container (see also *Containers for Injections* under *Injections* ⟨1⟩)—A multiple-dose container is a multiple-unit container for articles intended for parenteral administration only.

Storage Temperature—Specific directions are stated in some monographs with respect to the temperatures at which Pharmacopeial articles shall be stored, when stability data indicate that storage at a lower or a higher temperature produces undesirable results. Such directions apply except where the label on an article states a different storage temperature on the basis of stability studies of that particular formulation. The conditions are defined by the following terms.

Freezer—A place in which the temperature is maintained thermostatically between −20° and −10° (−4° and 14°F).

Cold—Any temperature not exceeding 8° (46°F). A *refrigerator* is a cold place in which the temperature is maintained thermostatically between 2° and 8° (36° and 46°F).

Cool—Any temperature between 8° and 15° (46° and 59°F). An article for which storage in a *cool place* is directed may, alternatively, be stored in a *refrigerator*, unless otherwise specified by the individual monograph.

Room Temperature—The temperature prevailing in a working area.

Controlled Room Temperature—A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25° (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°; and that allows for excursions between 15° and 30° (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses. Articles may be labeled for storage at "controlled room temperature" or at "up to 25°", or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variations. (See also *Stability* under *Pharmaceutical Dosage Forms* ⟨1151⟩.)

An article for which storage at *Controlled room temperature* is directed may, alternatively, be stored in a *cool place*, unless otherwise specified in the individual monograph or on the label.

Warm—Any temperature between 30° and 40° (86° and 104°F).

Excessive Heat—Any temperature above 40° (104°F).

Protection from Freezing—Where, in addition to the risk of breakage of the container, freezing subjects an article to loss of strength or potency, or to destructive alteration of its characteristics, the container label bears an appropriate instruction to protect the article from freezing.

Storage under Nonspecific Conditions—For articles, regardless of quantity, where no specific storage directions or limitations are provided in the individual monograph, it is to be understood that conditions of storage and distribution include protection from moisture, freezing, and excessive heat.

Labeling—The term "labeling" designates all labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term "label" designates that part of the labeling upon the immediate container.

A shipping container, unless such container is also essentially the immediate container or the outside of the consumer package, is exempt from the labeling requirements of this Pharmacopeia.

Articles in this Pharmacopeia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the Pharmacopeial requirements set forth for the articles.

Amount of Ingredient per Dosage Unit—The strength of a drug product is expressed on the con-

tainer label in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling.

Pharmacopeial articles in capsule, tablet, or other unit dosage form shall be labeled to express the quantity of each active ingredient or recognized nutrient contained in each such unit. Pharmacopeial drug products not in unit dosage form shall be labeled to express the quantity of each active ingredient in each milliliter or in each gram, or to express the percentage of each such ingredient (see *Percentage Measurements*), except that oral liquids or solids intended to be constituted to yield oral liquids may, alternatively, be labeled in terms of each 5-milliliter portion of the liquid or resulting liquid. Unless otherwise indicated in a monograph or chapter, such declarations of strength or quantity shall be stated only in metric units (see also *Units of Potency* in these *General Notices*.

In order to help minimize the possibility of errors in the dispensing and administration of drugs, the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero (e.g., express as 4 mg [not 4.0 mg]). The quantity of active ingredient when expressed as a decimal number smaller than one shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg [not .2 mg]).

Labeling of Salts of Drugs—It is an established principle that Pharmacopeial articles shall have only one official name. For purposes of saving space on labels, and because chemical symbols for the most common inorganic salts of drugs are well known to practitioners as synonymous with the written forms, the following alternatives are permitted in labeling official articles that are salts: HCl for hydrochloride; HBr for hydrobromide; Na for sodium; and K for potassium. The symbols Na and K are intended for use in abbreviating names of the salts of organic acids; but these symbols are not used where the word Sodium or Potassium appears at the beginning of an official title (e.g., Phenobarbital Na is acceptable, but Na Salicylate is not to be written).

Labeling Vitamin-containing Products—The vitamin content of Pharmacopeial preparations shall be stated on the label in metric units per dosage unit. The amounts of vitamins A, D, and E may be stated also in USP Units. Quantities of vitamin A declared in metric units refer to the equivalent amounts of retinol (vitamin A alcohol). The label of a nutritional supplement shall bear an identifying lot number, control number, or batch number.

Labeling Parenteral and Topical Preparations—The label of a preparation intended for parenteral or topical use states the names of all added substances (see *Added Substances* in these General Notices, and see *Labeling* under *Injections* ⟨1⟩), and, in the case of parenteral preparations, also their amounts or proportions, except that for substances added for adjustment of pH or to achieve isotonicity, the label may indicate only their presence and the reason for their addition.

Labeling Electrolytes—The concentration and dosage of electrolytes for replacement therapy (e.g., sodium chloride or potassium chloride) shall be stated on the label in milliequivalents (mEq). The label of the product shall indicate also the quantity of ingredient(s) in terms of weight or percentage concentration.

Labeling Alcohol—The content of alcohol in a liquid preparation shall be stated on the label as a percentage (v/v) of C_2H_5OH.

Special Capsules and Tablets—The label of any form of Capsule or Tablet intended for administration other than by swallowing intact bears a prominent indication of the manner in which it is to be used.

Expiration Date—The label of an official drug product or nutritional supplement shall bear an expiration date. All articles shall display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background or sharply embossed, and easily understood (e.g., "EXP 6/89," "Exp. June 89," "Expires 6/89"). [NOTE—For additional information and guidance, refer to the Nonprescription Drug Manufacturers Association's *Voluntary Codes and Guidelines of the OTC Medicines Industry*.]

The monographs for some preparations state how the expiration date that shall appear on the label is to be determined. In the absence of a specific requirement in the individual monograph for a drug product or nutritional supplement, the label shall bear an expiration date assigned for the particular formulation and package of the article, with the following exception: the label need not show an expiration date in the case of a drug product or nutritional supplement packaged in a container that is intended for sale without prescription and the labeling of which states no dosage limitations, and which is stable for not less than 3 years when stored under the prescribed conditions.

Where an official article is required to bear an expiration date, such article shall be dispensed solely in, or from, a container labeled with an expiration date, and the date on which the article is dispensed shall be within the labeled expiry period. The expiration date identifies the time during which the article may be expected to meet the requirements of the Pharmacopeial monograph provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the article may be dispensed or used. Where an expiration date is stated only in terms of the month and the year, it is a representation that the intended expiration date is the last day of the stated month.

For articles requiring constitution prior to use, a suitable beyond-use date for the constituted product shall be identified in the labeling.

In determining an appropriate period of time during which a prescription drug may be retained by a patient after its dispensing, the dispenser shall take into account, in addition to any other relevant factors, the nature of the drug; the container in which it was packaged by the manufacturer and the expiration date thereon; the characteristics of the patient's container, if the article is repackaged for dispensing; the expected storage conditions to which the article may be exposed; and the expected length of time of the course of therapy. Unless otherwise required, the dispenser may, on taking into account the foregoing, place on the label of a multiple-unit container a suitable beyond-use date to limit the patient's use of the article. Unless otherwise specified in the individual monograph, such beyond-use date shall be not later than (a) the expiration date on the manufacturer's container, or (b) one year from the date the drug is dispensed, whichever is earlier.

VEGETABLE AND ANIMAL SUBSTANCES

The requirements for vegetable and animal substances apply to the articles as they enter commerce; however, lots of such substances intended solely for the manufacture or isolation of volatile oils, alkaloids, glycosides, or other active principles may depart from such requirements.

Statements of the distinctive microscopic structural elements in powdered substances of animal or vegetable origin may be included in the individual monograph as a means of determining identity, quality, or purity.

Foreign Matter—Vegetable and animal substances are to be free from pathogenic organisms (see *Microbiological Attributes of Nonsterile Pharmaceutical Products* ⟨1111⟩), and are to be as free as reasonably practicable from microorganisms, insects, and other animal contamination, including animal excreta. They shall show no abnormal discoloration, abnormal odor, sliminess, or other evidence of deterioration.

The amount of foreign inorganic matter in vegetable or animal substances, estimated as *Acid-insoluble ash*, shall not exceed 2 percent of the weight of the substance, unless otherwise specified in the individual monograph.

Before vegetable substances are ground or powdered, stones, dust, lumps of soil, and other foreign inorganic matter are to be removed by mechanical or other suitable means.

In commerce it is seldom possible to obtain vegetable substances that are without some adherent or admixed, innocuous, foreign matter, which usually is not detrimental. No poisonous, dangerous, or otherwise noxious foreign matter or residues may be present. Foreign matter includes any part of the plant not specified as constituting the substance.

Preservation—Vegetable or animal substances may be protected from insect infestation or microbiological contamination by means of suitable agents or processes that leave no harmful residues.

WEIGHTS AND MEASURES

The International System of Units (SI) is used in this Pharmacopeia. The SI metric and other units, and the symbols commonly employed, are as follows.

Ci = curie
mCi = millicurie
μCi = microcurie
nCi = nanocurie

Mrad = megarad

m = meter
dm = decimeter
cm = centimeter
mm = millimeter
μm = micrometer (0.001 mm)
nm = nanometer*
kg = kilogram
g = gram **
mg = milligram
μg; mcg = microgram†
ng = nanogram
pg = picogram
dL = deciliter
L = liter
mL = milliliter; ‡
μL = microliter

Eq = gram-equivalent weight (equivalent)
mEq = milliequivalent
mol = gram-molecular weight (mole)
Da = dalton (relative molecular mass)
mmol = millimole
Osmol = osmole
mOsmol = milliosmole
Hz = hertz
kHz = kilohertz
MHz = megahertz
MeV = million electron volts
keV = kilo-electron volt
mV = millivolt
psi = pounds per square inch
Pa = pascal
kPa = kilopascal
g = gravity (in centrifugation)

* Formerly the symbol mμ (for millimicron) was used.

** The gram is the unit of mass that is used to measure quantities of materials. Weight, which is a measure of the gravitational force acting on the mass of a material, is proportional to, and may differ slightly from, its mass due to the effects of factors such as gravity, temperature, latitude, and altitude. The difference between mass and weight is considered to be insignificant for compendial assays and tests, and the term "weight" is used throughout *USP* and *NF*.

† Formerly the abbreviation mcg was used in the Pharmacopeial monographs; however, the symbol μg now is more widely accepted and thus is used in this Pharmacopeia. The term "gamma," symbolized by γ, is frequently used for microgram in biochemical literature.

NOTE—The abbreviation mcg is still commonly employed to denote microgram(s) in labeling and in prescription writing. Therefore, for purposes of labeling, "mcg" may be used to denote microgram(s).

‡ One milliliter (mL) is used herein as the equivalent of 1 cubic centimeter (cc).

The International System of Units (SI) is also used in all radiopharmaceutical monographs. The symbols commonly employed are as follows.

Bq = becquerel
kBq = kilobecquerel
MBq = megabecquerel
GBq = gigabecquerel
Gy = gray
mGy = milligray

CONCENTRATIONS

Molal, molar, and normal solution concentrations are indicated throughout this Pharmacopeia for most chemical assay and test procedures (see also *Volumetric Solutions* in the section, *Reagents, Indicators, and Solutions*). Molality is designated by the symbol *m* preceded by a number that is the number of moles of the designated solute contained in one kilogram of

the designated solvent. Molarity is designated by the symbol *M* preceded by a number that is the number of moles of the designated solute contained in an amount of the designated solvent that is sufficient to prepare one liter of solution. Normality is designated by the symbol *N* preceded by a number that is the number of equivalents of the designated solute contained in an amount of the designated solvent that is sufficient to prepare one liter of solution.

Percentage Measurements—Percentage concentrations are expressed as follows:

Percent weight in weight—(w/w) expresses the number of g of a constituent in 100 g of solution or mixture.

Percent weight in volume—(w/v) expresses the number of g of a constituent in 100 mL of solution, and is used regardless of whether water or another liquid is the solvent.

Percent volume in volume—(v/v) expresses the number of mL of a constituent in 100 mL of solution.

The term *percent* used without qualification means, for mixtures of solids and semisolids, percent weight in weight; for solutions or suspensions of solids in liquids, percent weight in volume; for solutions of liquids in liquids, percent volume in volume; and for solutions of gases in liquids, percent weight in volume. For example, a 1 percent solution is prepared by dissolving 1 g of a solid or semisolid, or 1 mL of a liquid, in sufficient solvent to make 100 mL of the solution.

In the dispensing of prescription medications, slight changes in volume owing to variations in room temperatures may be disregarded.